REMARKS

Telephone Interview:

Applicants would like to express their appreciation to Examiner Zeman for the courtesy extended to Applicants' agent, Angela Dallas Sebor, during the telephone interview of July 21, 2003. During the interview, the remaining rejection under 35 U.S.C. § 112, first paragraph, was discussed. Dr. Sebor discussed with the Examiner the examples in the specification that demonstrate the use of the claimed immunoregulatory composition with the antigen MUC1 and peritoneal exudate cells (PECs, wherein macrophages are the primary mannose receptor bearing cells) and that show the effectiveness of the vaccine in inducing an immune response *in vivo* in experiments. Dr. Sebor also discussed the Declaration of Dr. Pietersz which demonstrates the use of an antigen other than MUC1 (CRIPTO) in conjunction with a different cell type, dendritic cells, and shows the effectiveness of the vaccine in inducing an immune response *in vivo* in mice. Dr. Sebor explained that these were all *in vivo* experiments and that the use of cytokine assays to evaluate the *in vivo* response is a common measurement of an immune response. The Examiner suggested that a showing of elicitation of an immune response using at least one additional antigen in the claimed composition, and preferably, an antigen that is divergent from the MUC1 and CRIPTO antigens, would be positive evidence toward a broader claim scope. The Examiner also suggested that Applicants address the issue of what type of cell bears mannose receptors.

Claim Amendments:

Claims 71 and 72 have been added to more particularly describe embodiments of the invention. Support for Claim 71 is found in the specification on page 16, lines 1-3. Support for Claim 72 is found in the specification on page 6, lines 21-22.

Objection to the Specification and Rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has maintained the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, the Examiner states that the specification is enabling for immunoregulatory compositions comprising mannose receptor bearing cells and a conjugate comprising MUC1 and a carbohydrate polymer comprising mannose,

where the carbohydrate polymer is a fully oxidized carbohydrate polymer comprising free aldehydes. However, the Examiner contends that the specification does not enable immunoregulator compositions comprising any antigen. In response to Applicants' last response, the Examiner contends that Applicants prior arguments did not address compositions that fall within the scope of the claims since they allegedly addressed the effects of the antigen conjugate only, in the absence of the mannose receptor bearing cells. The Examiner contends that the data provided by Dr. Pietersz demonstrates the *ex vivo* pulsing of a single cell type (dendritic cells) using a single antigen (CRIPTO) and the ability of splenocytes from mice immunized with the vaccine to produce IFN-γ *in vitro*. The Examiner contends that the data fails to demonstrate that any of the claimed antigens can be used and induce an immune response *in vivo*. The Examiner also asserts that the data provided by Dr. Pietersz is non-persuasive since it is allegedly unclear whether the CRIPTO antigen used in the experiments presented in the Declaration was coupled to fully oxidized mannan.

Applicants traverse the rejection of the claims under 35 U.S.C. § 112, first paragraph. First, with regard to the scope of the antigen in the composition, as Applicants' agent discussed with the Examiner in the July 21 interview, Applicants have provided evidence that at least two different antigens can be used in the claimed conjugate and composition which, when administered *in vivo* to an animal, elicits an antigen-specific immune response. Therefore, to limit the claims to only MUC1 would be unduly limiting since Applicants have demonstrated enablement for the invention beyond the use of MUC1. As discussed previously, the data taken as a whole indicate that the claimed composition will induce an *in vivo* cellular immune response, regardless of what immunizing antigen is used, since it is the combination of the mannose receptor bearing cells and the oxidized carbohydrate polymer comprising mannose and aldehyde groups in the conjugate that serves as an effective adjuvant for an antigen that is conjugated to the oxidized carbohydrate polymer. The mechanism of enhancing the immune response is provided by the constant factors in the composition of the mannose receptor bearing cells and the oxidized carbohydrate polymer comprising mannose and aldehyde groups in the conjugate and therefore, it would be expected by those of skill in the art that the use of any immunogen in the context of the claimed composition would elicit an immunogen-specific immune response.

In further support of the claimed invention, Applicants submit herewith a post-filing publication by some of the present inventors and their colleagues (Davis et al., 2002, *Ann. N.Y. Acad.*

Sci. 969:119-125) which shows that in a bovine vaccine model, pulsing of macrophages with a conjugate comprising oxidized mannan and a parasitic antigen, a peptide from *Anaplasma marginale* MSP-1, results in the alteration of cytokine production by the macrophages and particularly, in an increase in production of inflammatory mediators and immune response regulators: IL-1β, IL-6, IL-10, IL-12, IL-18 and TNF-α. Production of such cytokines can create a microenvironment conducive to the stimulation of T cell responses. Therefore, this data further supports the predictability of the use of the claimed composition with any suitable immunizing antigen. Finally, Applicants are in the process of preparing additional data showing the use of a composition according to the invention that includes yet another antigen, that could be submitted by Supplemental Response.

Second, with regard to the type of mannose receptor bearing cell used in the composition, Applicants have also demonstrated that at least two different cell types (peritoneal exudate cells/macrophages and dendritic cells) can be successfully used in the composition of the invention. As discussed in the specification, the present invention is advantageous in that the composition delivers an antigen to the MHC class I pathway for presentation by class I molecules, thereby inducing cytotoxic T lymphocytes and TH1 cytokine production. Applicants submit that any mannose receptor bearing cell that is capable of delivering an antigen to the MHC class I pathway for MHC class I antigen presentation and ultimate induction of cytotoxic T lymphocytes (i.e generation of a cellular immune response) will be suitable for use in accordance with the invention. The features of the mannose receptor and cellular immune response are already recited in the claims. The mannose in the conjugate of the oxidized carbohydrate polymer and antigen targets the conjugate into the mannose receptor bearing cell by binding to the receptor. Upon entry of the conjugate, the antigen is processed by the cell and presented by the MHC class I pathway. Most cells express MHC class I and therefore, any cell that meets the claim limitations of bearing a mannose receptor can be considered for use in a composition of the invention. Therefore, given the teachings and the data provided by the specification and the Declarations of Dr. Pietersz, Applicants submit that the specification has enabled the use of any suitable mannose receptor bearing cell in the claimed composition.

With regard to the Examiner's concerns regarding the data presented in the last filed Declaration of Dr. Pietersz, as discussed in the July 21 interview, the composition including the conjugate comprising CRIPTO and the dendritic cells was in fact administered to mice *in vivo*. The

composition itself was prepared by mixing the cells and conjugate *ex vivo*, but the composition was then used *in vivo* and efficacy was shown. The demonstration of the antigen-specific immune response in a controlled *in vitro* assay after immunization is a perfectly valid means of showing the effects of the *in vivo* immunization protocol. Second, the Examiner states that it was unclear whether the CRIPTO antigen used in the experiments presented in the Declaration was coupled to fully oxidized mannan. However, Applicants note that the Declaration states that a conjugate of mannan-Cripto "prepared as described in the present application" was used in the experiment. The present application describes the preparation of oxidized-mannan fusion proteins, and since this Declaration was presented in support of claims to fully oxidized mannan, it was assumed that it would be understood that the conjugate of mannan-CRIPTO utilized fully oxidized mannan. If required by the Examiner, Applicants can provide a Supplemental Declaration to confirm this point.

In summary, Applicants submit that the evidence of record supports Applicants' position that the claims are fully enabled as currently amended. Therefore, the Examiner is respectfully requested to withdraw the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph.

Applicants have attempted to address all of the Examiner's concerns as set forth in the May 19 Office Action, and it is submitted that the claims are in a condition for allowance. In the event that the Examiner has any questions regarding Applicants' position, please consider this to be a provisional request for a telephone interview with the below-named agent.

Respectfully submitted,

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